57. The method of claim 56 wherein the activity of the polypeptide that is modulated is G-protein-mediated signal transduction activity.

58. A method for identifying a compound that modulates the activity of a polypeptide comprising the amino acid sequence set forth as amino acids 6 to 370 of SEQ ID NO:1, the method comprising contacting a cell expressing the polypeptide with a test compound under conditions such that the test compound can modulate the activity of the polypeptide and assessing the activity of the polypeptide to thereby determine if the test compound is a compound that modulates the activity of the polypeptide, wherein the cell is selected from the group consisting of brain cells, spleen cells, lung cells, kidney cells, skeletal muscle cells, liver cells, and heart cells.

59. The method of claim 58 wherein the activity of the polypeptide that is modulated is G-protein-mediated signal transduction activity.

REMARKS

Status of the Claims:

Claims 32-59 are pending in the current application. Claims 17-19 and 21-31 have been cancelled without prejudice. New claims 32-59 have been added. New claim 32 encompasses subject matter previously encompassed by clause (a) of claim 19. Support for new claims 33, 38, 43, and 48 may be found on page 39, lines 16-19 of the specification. New claims 34, 39, 44, and 49 encompass subject matter previously encompassed by claim 21. New claims 35, 40, 45, and 50 encompass subject matter previously encompassed by claim 22. Support for new claims 36, 41, 46, 51, 53, 55, 57, and 59 may be found on page 7, line 28 *et seq.* of the specification. Support for new claim 37 can be found in original claim 19 and page 13, lines 16-19 of the specification. New claim 42 encompasses subject matter previously encompassed by clause (e) of claim 19. New claim 47 encompasses subject matter previously encompassed by clause (g) of

claim 19. New claim 52 encompasses subject matter previously encompassed by clause (a) of claim 25. Support for new claim 54 can be found in original claim 25 and page 13, lines 16-19 of the specification. New claim 56 encompasses subject matter previously encompassed by clause (e) of claim 25. New claim 58 encompasses subject matter previously encompassed by clause (g) of claim 25. No new matter has been added by way of amendment.

Applicants affirm the election of Group VII and expressly reserve the right to file divisional applications or take such other appropriate measures deemed necessary to protect the inventions in the remaining species. Reexamination and reconsideration of the claims are respectfully requested.

Objections to the Drawings

In response to the Notice of Draftsperson's Patent Drawing Review attached to Paper Number 11, Applicants submit herewith one set (6 sheets) of formal drawings. Please substitute the new drawings for the originally filed drawings.

The Rejection Under 35 U.S.C. §101 Should be Withdrawn:

Claims 19 and 21-27 were rejected under 35 U.S.C. §101 on the grounds that the claimed invention is not supported by either a specific asserted utility or a well-established utility. This rejection is respectfully traversed as applied to new claims 32-59 for the reasons described below.

14926 Encodes a G-Protein Coupled Receptor.

The 14926 polypeptide has been compared to the Pfam database of protein families and been shown to share a high degree of sequence similarity with the consensus domain for the 7 transmembrane receptor rhodopsin family of G-protein coupled receptors (PFAM Accession No. PF00001; see Figure 2). The Pfam database provides a curated collection of well-characterized protein family domains with high quality alignments. Functional domains of novel proteins may

be identified by comparison with the Pfam protein family domain alignments. It is well known in the art that regions of sequence homology with consensus domains characteristic of a family of proteins having a know function may be used to determine the function of a novel polypeptide. The proteins included in the Pfam seed alignment for the 7 transmembrane receptor consensus sequence include numerous GPCRs that have been well-characterized biochemically; for example the serotonin receptors $5HT_{1A}$, $5HT_{1B}$, and 5HT-7; the β-1 and α-2 adrenergic receptors; the dopamine receptor, and the muscarinic acetylcholine receptor M1. Accordingly, the presence of a Pfam 7 transmembrane domain rhodopsin family in the 14926 sequence indicates that 14926 functions a G-protein coupled receptor (GPCR).

14926 Has Specific, Substantial, and Credible Utility.

The Examiner has rejected the claims under 35 U.S.C. §101 on the grounds that the claimed receptor is useful only as a research tool. This does not correctly reflect the view in the art, where it is known that, "[h]istorically, the superfamily of GPCRs has proven to be among the most successful drug targets and consequently these newly isolated orphan receptors have great potential for pioneer drug discovery" (Stadel *et al.* (1997) *Trends Pharmacol. Sci.* 18:430-436; provided as Appendix A). Those of skill in the art recognize that the identification of a novel member of the G-protein coupled receptor family provides an immediate benefit. In addition to serving as reagents and molecular targets in the diagnosis and treatment of 14926-mediated disorders as described in the specification on page 24 *et seq.*, all members of the rhodopsin family of GPCRs have utility in selectivity screening of candidate drugs that target members of this family of GPCRs. It is known in the art that the clinical usefulness of a therapeutic compound is determined not only by its ability to bind and modulate a molecular target of interest, but also by its selectivity. Drugs that bind selectively to their molecular target are highly preferred over those that bind to structurally-related molecules, as the selective compounds are far less likely to have unwanted side effects in clinical use. Thus, an important component of any drug development strategy is determining the selectivity of the candidate drug for the molecular target of interest over structurally-related polypeptides. The effectiveness of selectivity screening

in uncovering interactions that may result in undesirable clinical side-effects increases in proportion with the number of structurally-related polypeptides screened. The usefulness of these structurally-related polypeptides is not dependent on their biological role or ligand-binding properties; their utility comes from the fact that they share significant sequence identity with the molecular target of the candidate drug.

One example of the use of orphan receptors in selectivity screening is found in Goodwin *et al.* (2000) *Molecular Cell* 6:517-526, a copy of which is provided as Appendix B. This reference is directed to the identification of a specific agonist for FXR, an orphan nuclear receptor that regulates bile acid synthesis and is a target in the treatment of cholestasis (Niesor *et al.* (2001) *Curr. Pharm. Des.* 7:231-259). The authors state that many previously-identified FXR ligands interact with other proteins including bile-acid-binding proteins and transporters (Goodwin *et al., ibid.*, page 518, column 1, first full paragraph). In order to identify a compound that selectively modulates FXR, the authors screened for compounds that modulated FXR activity and then tested these compounds for their ability to activate other nuclear receptors that share structural similarity with FXR. Figure 1C of Goodwin *et al.* shows that the compound GW4064 potently activates FXR but does not modulate the activity of the other nuclear receptors tested. Note that the nuclear receptor panel screened in Figure 1C includes the orphan nuclear receptors SHP-1 and LRH-1 in addition to receptors having previously-identified ligands.

Although more than 50% of prescription drugs act at GPCR targets, some of these drugs have efficacy problems and limiting side-effects because the compounds do not differentiate between receptor subtypes. Accordingly, because the rhodopsin family of GPCRs includes a number of key drug targets, members of this family share a common use in the selectivity screening of candidate drugs. The 14926 receptor shares a high degree of identity with a consensus domain characteristic of the rhodopsin family of GPCRs (see Figure 2). The rhodopsin family of GPCRs includes targets for the treatment of numerous disorders including depression, anxiety, migraine, asthma, hypertension, and cardiovascular disorders. Thus, all members of this important class of GPCRs, including those disclosed in the present invention,

have a specific, immediately available, real world utility in the selectivity screening of drugs directed at GPCR targets.

The United States Patent and Trademark Office "Utility Examination Guidelines" (66 Fed Reg. 1092 (2001)) make it clear that sequence homology is sufficient to establish utility, and that, contrary to the utility standard set by the Examiner, working examples or biochemical evidence are not a *per se* requirement for the establishment of utility. The "Utility Examination Guidelines" state, "[w]hen a patent application claiming a nucleic acid asserts a specific, substantial, and credible utility, and bases the assertion upon homology to existing nucleic acids or proteins having an accepted utility, the asserted utility must be accepted by the examiner unless the Office has sufficient evidence or sound scientific reasoning to rebut such an assertion." (66 Fed. Reg. 1096). In the present case, the Examiner has not accepted the asserted utility for the claimed invention but has failed to provide sufficient evidence or sound scientific reasoning to rebut Applicants' assertions.

In view of the above arguments, all grounds for rejection under 35 U.S.C. §101 have been overcome. Reconsideration and withdrawal of the rejection are respectfully requested.

The Rejections Under 35 U.S.C. §112, First Paragraph, Should be Withdrawn

Claims 19 and 21-27 have been rejected under 35 U.S.C. § 112, first paragraph on the grounds that the claimed invention is not supported by a specific asserted utility or a well established utility and therefore one skilled in the art would not know how to use the claimed invention so that it would operate as intended without undue experimentation. The rejection is traversed as applied to new claims 32-59. As discussed above, the claimed invention has both a specific and substantial asserted utility and a well-established utility, thereby overcoming the grounds of the rejection.

Claims 19 and 21-27 were rejected under 35 U.S.C. § 112, first paragraph, on the grounds that Applicants have not provided sufficient written description for the allelic variants and sequence variants recited in these claims. The rejection is respectfully traversed as applied to new claims 37-46 and 54-57 for the reasons described below.

Claims 37-46 and 54-57 meet the written description guidelines set forth in the "Guidelines for Examination of Patent Applications Under the 35 U.S.C. §112, ¶ 1, 'Written Description' Requirement" (66 Fed. Reg. 1099 (2001)). The guidelines state:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings...., or by disclosure of relevant identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus."

66 Fed. Reg. 1106. In the present case, the sequence variants recited in claims 37-46 and 54-57 have been described by both their structural properties (*i.e.* as having a given percent sequence identity with the amino acid sequence set forth in SEQ ID NO:2 or as being encoded by a nucleotide sequence that hybridizes to the nucleotide sequence set forth in SEQ ID NO:2 under stringent conditions) and functional characteristics (*i.e.* G-protein mediated signal transduction activity), thereby meeting the standards set forth in the guidelines. The present claims are comparable to the claim presented in Example 14 of the "Synopsis of Application of Written Description Guidelines" cited in the written description guidelines (66 Fed. Reg. 1101), in which the claimed protein is described by its sequence identity with a second protein and by its function. The analysis of this example in the Synopsis finds that the claimed polypeptide is adequately described. Similarly, in the present case the criteria for written description have been met as the nucleotide sequence is defined by structure and function and the rejection should not be applied to claims 37-46 and 54-57.

Claims 19 and 21-27 were rejected under 35 U.S.C. §112, first paragraph on the grounds that the Applicants have not provided sufficient written description for the "agent" or "test compound" recited in these claims. The rejection is respectfully traversed as applied to new claims 32-59.

New claims 32-51 recite compounds that that modulate the activity of a polypeptide, and new claims 52-59 recite "test compounds." The specification gives specific examples of classes of compounds that may be used in the claimed methods including peptides, phosphopeptides, antibodies, and small organic and inorganic molecules (page 25, lines 3-13). The use of 14926 antibodies to inhibit 14926 receptor function is described on page 39, lines 14-15 of the specification. Methods for determining whether a compound modulates the activity of a 14926 receptor polypeptide are given on page 24, line 14 *et seq.* and page 25, line 20 *et seq.* Accordingly, the specification provides classes of compounds that can be utilized in the claimed methods, functional and structural descriptions of the polypeptides to be modulated in the methods, and methods of assaying the activities modulated by the compounds. In view of the description provided, one of skill in the art would reasonably conclude that the Applicants had possession of the claimed invention.

Claims 19 and 21-27 were rejected under 35 U.S.C. §112, first paragraph, on the grounds that they recite a deposited sequence but fail to provide the corresponding deposit number. All references to a deposit have been deleted from the specification and the new claims, thereby overcoming the grounds of the rejection.

In view of the above arguments and amendments, all grounds for rejection under 35 U.S.C. §112, first paragraph, have been obviated or overcome. Reexamination and reconsideration of the claims are respectfully requested.

The Rejections Under 35 U.S.C. §112, Second Paragraph, Should be Withdrawn

Claims 19 and 25 have been rejected under 35 U.S.C. §112, second paragraph, on the grounds that they recite a deposited sequence but fail to give a deposit number. New claims 32-59 do not recite an ATCC deposit, thereby obviating the rejection.

Claim 19 was rejected under35 U.S.C. §112, second paragraph as being incomplete on the grounds that the method steps do not refer back to the preamble. The method steps of new claims 32, 37, 42, and 47 do refer back to the preamble, thereby obviating the rejection.

Claims 19 and 25 were rejected under 35 U.S.C. §112, second paragraph for reciting "the activity of the polypeptide," without defining what this activity is. The rejection is respectfully traversed as applied to new claims 32-59. The specification provides guidance regarding polypeptide activities to be modulated on page 7, line 28 *et seq.*, and on page 24, line 21 *et seq.* In view of the description of polypeptide activities provided in the specification, the metes and bounds of the claims would be clear to one of ordinary skill in the art.

Claims 19 and 25 were rejected under 35 U.S.C. §112, second paragraph, on the grounds that they recite "an agent" or "a compound" without providing the structural or physical characteristics. The rejection is respectfully traversed as applied to new claims 32-59. The specification gives specific examples of classes of compounds that may be used in the claimed methods including peptides, phosphopeptides, antibodies, and small organic and inorganic molecules (page 25, lines 3-13). The use of 14926 antibodies to inhibit 14926 receptor function is described on page 39, lines 14-15 of the specification. In view of the description of the compounds and test compounds provided in the specification, the scope of the claimed methods would be clear to one of ordinary skill in the art.

In view of the above arguments and amendments, all grounds for rejection under 35 U.S.C. §112, second paragraph, have been obviated or overcome. Reexamination and reconsideration of the claims are respectfully requested.

CONCLUSIONS

It is believe that all the rejections have been obviated or overcome and the claims are in condition for allowance. Early notice to this effect is solicited.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, Washington, DC 20231, on October 3, 2001.

Wendy Wagner

Version with Markings to Show Changes Made:

In the Specification:

Please amend the paragraph on lines 10-13 of page 4 as follows:

The invention provides isolated 14926 receptor polypeptides including a polypeptide having the amino acid sequence shown in SEQ ID NO:1[NO 1, or the amino acid sequence encoded by the cDNA deposited as ATCC No. _____ on _____ ("the deposited cDNA")].

Please amend the paragraph on lines 14-15 of page 4 as follows:

The invention also provides isolated 14926 receptor nucleic acid molecules having the sequence shown in SEQ ID NO:2[NO 2 or in the deposited cDNA].

Please amend the paragraph on lines 16-18 of page 4 as follows:

The invention also provides variant nucleic acid sequences that are substantially homologous to the nucleotide sequence shown in SEQ ID NO:2[NO 2 or in the deposited cDNA].

Please amend the beginning on line 18 or page 5 as follows:

Figure 1A and 1B show [shows]the 14926 nucleotide sequence (SEQ ID NO:2[NO 2]) and the deduced 14926 amino acid sequence (SEQ ID NO:1[NO 1]). It is predicted that amino acids 1-23 constitute the amino terminal extracellular domain, amino acids 24-341 constitute the region spanning the transmembrane domain, and amino acids 342-370 constitute the carboxy terminal intracellular domain. The transmembrane domain contains seven transmembrane segments, three extracellular loops and three intracellular loops. The transmembrane segments are found from about amino acid 24 to about amino acid 46, from about amino acid 56 to about amino acid 78, from about amino acid 96 to about amino acid 117, from about amino acid 133 to about amino acid 154, from about amino acid 185 to about amino acid 209, from about amino acid 286 to about amino acid 307, and from about amino acid 318 to about amino acid 341. Within the region spanning the entire transmembrane domain are three intracellular and three

extracellular loops. The three intracellular loops are found from about amino acid 47 to about amino acid 55, from about amino acid 118 to about amino acid 132, and from about amino acid 210 to about amino acid 285. The three extracellular loops are found at from about amino acid 79 to about amino acid 95, from about amino acid 155 to about amino acid 184, and from about amino acid 308 to about amino acid 317.

Please amend the paragraph beginning on line 26 of page 6 as follows:

Figure 5A and 5B show [shows] an analysis of the 14926 open reading frame for amino acids corresponding to specific functional sites. A glycosylation site is found at amino acids 3-6, which corresponds to the amino terminal extracellular domain. A second glycosylation site is found at amino acids 83-86, which corresponds to the first extracellular loop. A third glycosylation site is found at amino acids 182-185, which spans the second extracellular loop and fifth transmembrane segment. A fourth glycosylation site is found at amino acids 227-230, which corresponds to the third intracellular loop. A fifth glycosylation site occurs at amino acids 264-267, also in the third intracellular loop. A cyclic AMP or cyclic GMP-dependent protein kinase phosphorylation site is found at amino acids 131-134 and spans the second intracellular loop and fourth transmembrane segment, and at amino acids 281-284, corresponding to the third intracellular loop. A protein kinase C phosphorylation site is found at amino acids 80-82, corresponding to the first intracellular loop. A second protein kinase C phosphorylation site is found at amino acids 93-95, corresponding to the first extracellular loop. A third protein kinase C phosphorylation site is found at amino acids 130-132, corresponding to the second intracellular loop. A fourth protein kinase C phosphorylation site is found at amino acids 178-180, corresponding to the second extracellular loop. A fifth protein kinase C phosphorylation site is found at amino acids 266-268, corresponding to the third intracellular loop. A sixth protein kinase C phosphorylation site is found at amino acids 342-344, corresponding to the carboxy terminal intracellular domain. A casein kinase II phosphorylation site occurs at amino acids 342-345, corresponding to the carboxy terminal intracellular domain. N-myristoylation sites occur at amino acids 84-89 and 90-95, corresponding to the first extracellular loop; 101-106,

corresponding to the third transmembrane segment; 237-242 and 258-263, corresponding to the third intracellular loop; and 318-323, corresponding to the seventh transmembrane segment. An amidation site is found at amino acids 266-269, corresponding to the third intracellular loop. In addition, amino acids corresponding in position to the GPCR signature and containing the invariant arginine are found in the sequence TRY at amino acids 118-120.

Please amend the paragraph on lines 4-6 of page 10 as follows:

The invention thus relates to a novel GPCR having the deduced amino acid sequence shown in Figure 1A and 1B (SEQ ID NO:1)[NO 1) or having the amino acid sequence encoded by the deposited cDNA, ATCC No. _____].

Please amend the paragraph on lines 12-16 of page 10 as follows:

The "14926 receptor polypeptide" or "14926 receptor protein" refers to the polypeptide in SEQ ID NO:1[NO 1 or encoded by the deposited cDNA]. The term "receptor protein" or "receptor polypeptide", however, further includes the numerous variants described herein, as well as fragments derived from the full length 14926 polypeptide and variants.